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(21) International Application Number: PCT/FI97/00208 (22) International Filing Date: 3 April 1997 (03.04.97) (30) Priority Data: 961492 3 April 1996 (03.04.96) FI 961493 3 April 1996 (03.04.96) FI (71)(72) Applicants and Inventors: HAKALEHTO, Elias [FI/FI]; Kasarminkatu 12 C 1, FIN-70110 Kuopio (FI). KURONEN, Ilpo [FI/FI]; Saarijärventie 6 F 43, FIN-70460 Kuopio (FI). (74) Agent: PITKÄNEN, Hannu; Savilahdentie 6 L 3, FIN-70210 Kuopio (FI).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU. ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> <i>In English translation (filed in Finnish).</i>

(54) Title: THERAPEUTIC AND PREVENTIVE METHOD AGAINST HARMFUL MICROBES**(57) Abstract**

The object of the invention is a therapeutic and preventive method against harmful microbes and substances, where the antibody is produced in eggs from whose yolk it is isolated. According to the method of the invention the antibody specific to the harmful microbes or substances is brought into the mouth and pharyngeal area in the form of product, which is either sucked or chewed or in a liquid form or as a cream or an emulsion.

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THERAPEUTIC AND PREVENTIVE METHOD AGAINST HARMFUL MICROBES

The object of the invention is therapeutic and preventive method against harmful microbes and substances.

Nature has its own probiotic components like antibodies. Antibodies are proteins produced by the organism and they are found in all more developed animals. The task of antibodies in the organism is to serve as the primary defensive mechanism against unknown components like microbes that penetrate to the organism. Antibodies are consisting of four polypeptide chains that form the functional molecule, which includes two specific identifying and binding sites and a separate frame that contains other biological functions. The most important property of the antibodies is their ability to bind to their target molecules very specifically. This means that with the help of antibodies it is possible to identify and eliminate e.g. only the harmful organisms. The organism defends against the penetrating microbes by forming antibodies that bind to the penetrator. The unique abilities of the antibodies to bind specifically to the desired molecules or structures taking part in eliminating the structure or destroying its ability to cause diseases either directly or indirectly, provide an excellent possibility for exploiting antibodies in strengthening the defensive mechanism of the organism or in making use of completely new mechanisms in preventing, diagnosing and healing the diseases. The formation of antibodies in sufficient amounts takes from several days to even weeks, however. During that time diseases may break out. In the course of infection the level of antibodies rises and at last the penetrator will be eliminated. In a similar way it takes a few weeks after the infection is over before the level of antibodies declines to the normal.

The ability of antibodies to identify their target molecules very specifically has been exploited in biomedical research and in the diagnosis of diseases already during several decades. Antibodies have become inevitable tools. In addition to research and diagnostics, the so called therapeutic purposes have become the object of new research efforts, where the antibodies introduced from outside to the organism would function in a similar way as the antibodies produced by the organism. In microbial diseases, for example, additional antibodies that come outside the organism will give an extra and fast protection against the penetrator and e.g. in spite of the slow mechanism of the organism to produce antibodies, the disease will not break out. The applications of the so-called therapeutic antibodies are very broad including all the

forms of operation to which the organism's own immune system is directed. The classic example of the therapeutic use of antibodies is the use of horse serum for acutely healing of difficult snakebites.

- 5 The problems in the widespread use of antibodies for controlling diseases are the cost of antibody production and the demands of their purity and structure. The applications with antibodies produced in the serum of warm-blooded animals include risks for human health because these are blood-products. Their use may cause life threatening reactions.

- 10 The production of antibodies in hen is at the moment reliable, safe and cheap alternative for antibodies that have been produced in earlier times in different mammals. Antibodies produced in hens have been used with good results in immunotherapy and in the detection methods based on the use of antibodies. This is based e.g. on effective methods that have been developed for the purification of antibodies from the egg yolk. Because the treatment of chicken does not demand
15 neither special circumstances nor particularly blood samples, hens are more suitable from the legislative point of view as test animals, for the only treatment is normal vaccination, in other words, increasing the excretion of desired antibodies to the egg yolk. Components that have been isolated from an egg can not be considered as blood
20 products, and therefore health risks included in blood products can be avoided.

- Antibodies against many kinds of antigens have been produced in hens. These include proteins, synthetic proteins, viruses of plants and wall structures of fungal and
25 bacterial cells. Hens have been found to be very effective producers of antibodies. A chicken that has been immunized, produces as much antibodies per month as is found in a high titre rabbit antiserum. Specific antibodies can be usually isolated from the egg yolk already after two weeks from the first immunization. The production of antibodies in hen continues at least 100 days. One egg can produce as much as about
30 10 doses of therapeutic antibodies. The costs per dose is much lower than e.g. in the production of monoclonal antibodies for the same purpose.

- The microbial material (originating e.g. from bacteria or viruses), which can be inactivated with radioactive irradiation, if required, is injected to the test animals like
35 hens for the production of adequate amounts of antibodies. Antibodies that have been isolated from the egg yolk for different kind of curing, preventive and other probiotic effects can be advantageously purified before their ultimate use. Effective methods

for the purification of these antibodies have been developed recently.

Mucous membranes of respiratory tract provide a very good gateway to the organism for many harmful microbes. Air that we breath and food bring along micro-organisms which attach to the mucous membranes of respiratory tract or different parts of alimentary tract from where they penetrate to the organism and cause the actual infection and the outbreak of a disease. The organism tries to defend against the invaders by secreting immunoglobulins A and E (IgA, IgE) to mucous membranes. The task of the IgA and IgE is to bind to the harmful organisms and by that way to prevent their penetration from mucous membranes to the body or to prevent their binding to the cellular tissue of the mucous membranes, which often precedes microbial infection. The mechanism mediated by IgA and IgE is not always enough to protect the body against the organisms coming from outside. One reason for this is a so called delay in the mechanism, because the secretion of a large amount of antibodies to the mucous membranes needs a contact with the antigen and requires many days for synthesis. During that period of time the amount of micro-organisms inside the body has become adequate for the outbreak of disease. In the course of the disease antibodies are secreted to blood circulation where they destroy the invader and also to the mucous membranes where they prevent the invasion of new organisms. When external antibodies are applied to the mucous membranes they will help the organism in eliminating the invading micro-organism. Potential uses for the additional antibodies that are given to the organism from outside are e.g.

- infection of the digestive tract or the respiratory tract in general
- dental caries
- influ enza and other respiratory viruses
- ear infections

Dental caries, for example, has been prevented efficiently in rats by using a therapeutic antibody that has been produced in the egg yolk.

Infections of respiratory tract with their secondary complications can cause diseases particularly for children and aged people. These disease are expensive to treat and take also much time. In the nasal cavity, auditory tube and trachea, there are cilia, whose rhythmic movement transports rheum together with harmful substances and particles to the pharynx where they are swallowed. This mechanism is an important part of the organism's defence system. Even a mild infection in the respiratory tract

destroys their cilia, whose recovery takes about 4-6 weeks. During this period the patient is more liable to new infections, which may lead him to a chain of diseases. With the help of adequate amount of antibodies that have been directed correctly, this can be avoided. At the moment there is not any reliable or cheap way to spread
5 antibodies to the upper area of the respiratory tract.

The purpose of this invention is to introduce a method which can be used for spreading antibodies to the area of mouth and pharynx and other respiratory organs in a efficient and cost-effective way.

10 The purpose of the invention will be achieved with the method described in the patent claims.

In the method according to the invention, the exploited antibody or microbe will be transported to the area of mouth and pharynx in a product that will be either sucked or chewed or is in a liquid form. The functioning of a probiotic microbial strain can be promoted by regulating the physical, chemical or biological parameters of mucous membranes or the part of the organism under treatment in a way that the conditions for the probiotic microbe will improve without hampering the normal function of the
15 mucous membranes or the part of the system. It is possible to e.g. add beneficial growth factor for the microbe in question or harmful substances for the competing microbes together with the probiotic microbe. It may be especially useful to regulate either the pH of the mucous membranes or the pH of the product that will be taken or both when using antibodies in order to keep the therapeutic antibodies as active as possible in the organism. Antibodies that have been given to mucous membranes have been found to posses protective influences against many pathogenic bacteria and even viruses. The basic idea of the method of this invention is to get antibodies that have been produced in the egg yolk either in a purified or unpurified form to the mucous membranes of mouth, pharynx and other upper respiratory tract or to the skin surface
20 in a way, that beneficial health effects for human being and test animals will be achieved. In this way the spread of infection in the lungs and ears will be prevented.

According to the invention the antibodies beneficial for health can be placed to candy products in such a form that they are e.g. released when sucking a caramel, biting a
25 chewing gum or in the liquid form liberating slowly from another kind of product, having thus a relatively long-lasting effects on the membranes of the upper respiratory

tract. In this procedure antibodies will dissolve slowly into the mucous membranes of mouth and pharynx and they give a more effective, more meaningful and long-lasting influence. If used repeatedly they can prevent the spreading of microbes through nose/pharynx tract to the auditory tract. Antibodies produced in eggs can be added to the product e.g. after purification in lyophilized form. It is beneficial for all probiotic influences if they can be directed to the desired parts of the organism, to the target molecules or to the microbes that must be prevented. In this process of directing antibodies it is possible to exploit mannose, that is situated naturally in the immunoglobulins of yolk. Many adhesive properties of microbes are directed to this sugar molecule (e.g. type 1-fimbria). With the aid of these molecules that are able to recognize their targets, it is possible to add to the antibodies also cells or molecules which facilitate their binding to the desired receptor molecules in the organism.

Using so called lyophilized antibodies it is possible to supplement dry products like sweets. Then the objects can be such as *Streptococcus mutans* that causes caries, viruses that cause influenza and other infections of upper respiratory tract, and other sources of infections of ears and lungs.

When exploiting the method according to the invention the egg yolk antibodies can be made reactive with probiotic microbial strain, which has the ability to bind antibodies through the mannose residue which is situating in the Fc-part. In natural conditions e.g. enteric bacteria with type 1-fimbria bind to this sugar molecule. If necessary, the same ability can be produced with the help of gene transfer methods by adding the required part of protein to the surface protein of the microbe in use (e.g. flagellin or S-layer protein). Then there will be formed a layer of recognizable antibody onto the surface of the probiotic microbe which helps the probiotic influences to be directed to the desired parts of the organism, cell surfaces, other microbial cells etc.

It can be found in the literature that antibodies can transport and attach to the target cells or tissues radionuclides, enzymes, genes, medically effective molecules or toxins. By using the method based on this invention it is possible to get microbial cells having a curative or probiotic use, easily into such a form that they are directed to the right place, where their beneficial effects for health are expected.

Antibodies produced in the egg yolk can be produced against e.g. influenza, parainfluenza, RSV-, adeno-, rhino-, EBV-, or cytomegaloviruses, rota- or

enteroviruses, bacteria that cause inflammation of ear or diseases of the respiratory tract, microbes that cause teeth diseases (e.g. *Streptococcus mutans*) or other microbes that produce harmful substances in the body. These antibodies can be produced also to eliminate influences of toxins and other substances that can be either toxic or harmful (e.g. environmental toxins). With the help of this method it is possible to increase the washing out of harmful organisms from the body when they bind themselves through antibodies either to each other or to carrier molecules or to particles or to corresponding substances. They can also prevent the function of the microbe or its reproduction e.g. by preventing transport of molecules through the cell wall, moving or binding of the microbial cells or they can disturb the microbial cell division. They can also aggregate the microbes in a way that they wash out from the body as larger particles or get into places where they are destroyed (e.g. the microbes of the pharynx in the circumstances of low pH in the stomach).

It is possible to join molecules to the health-promoting antibodies using so called coupling methods in order to make them more effective or to facilitate their transport to the desired object tissues in the organism. Molecules of that kind can be e.g. antibiotics, lectins, components that inhibit or stimulate growth of certain microbes, enzymes, cofactors or other corresponding molecules. The binding of these components to the antibodies can be accomplished with different methods either chemically or physically.

In one useful application of this invention antibody will be placed in the form of liquid, emulsion or cream on the surface or inside a nipple. On a nipple there are paths, clefts, semipermeable surfaces or other corresponding structures through which the liquid, emulsion or cream can seep to the mouth when the nipple is sucked. The material of the mouth-piece of the nipple can also be selected in way that it lets the antibody solution to penetrate and makes thus it possible for it to seep into the mouth. With this fashion antibodies can be given even to babies in a reliable and safe way. The liquid that contains the antibody has been advantageously sweetened with a suitable sweetening agent and the liquid is situated inside the nipple. The pH of the liquid can be regulated to the value desired. The nipple can be made for a single use or its base may have a cover that can be opened, and from where the antibody solution can be filled into the nipple.

When producing sweets or sweetened solutions or corresponding products containing therapeutic antibodies it is important to proceed in a way that the antibodies will not

be injured or destroyed during the production phase or in the storage. Therefore, it is important to control the temperature, pH and corresponding parameters in an optimal way. It is possible to add antibodies to the sweets in a solution that e.g. is buffered, containing trehaloses or other molecules protecting the antibodies from the effects of high temperatures.

Example 1

Antibodies were produced in a hen (A) by injecting it with a peptide consisting of the 29 N-terminal amino acids of the human parathyroid hormone. The antibodies produced against this peptide were isolated and purified from the egg yolk laid by the hen A according to previously known procedure.

The above mentioned antibodies containing product were added to the filled cherry confection (Ginja-cherry chocolate candy, Regina, Portugal) in a way that firstly the filling of the confection was partially removed with a sterile syringe and a sterile needle Microlance® 3 (length of the needle 50 mm, diameter 1,2 mm) and it was replaced by an antibody solution prepared in the sterile saline, and containing 25 mg of specific antibodies per 0,4 ml of the solution. The weight of the confection was 15,3 g and pH in a crushed form 4,95.

The confection was given to the test person to be consumed by smelting it in the mouth. After 5 minutes he was given 10 ml sterile saline solution for rinsing the mouth for 30 seconds and then spit to the sampling dish. After mixing a 50 µl sample was taken, which was mixed in 50 µl of Assay-buffer. Thereafter the detection was carried out with a peroxidase labeled antichickens antibody (Zymed Inc., CA, USA). An untreated candy and a liquid that was obtained in a similar way as the sample itself was used as a blank sample.

The results can be seen in Fig. 1.

Example 2

25 mg of antibodies produced according to the example 1 was added to the marmalade candy (Vihreä kuula, Fazer, Helsinki, Suomi) by removing corresponding amount of the marmalade from inside of the candy and joining the parts together again. The weight of the marmalade candy was 21,5 g and pH 3,51.

The marmalade candy containing the antibody was given to the test person. The sample was taken and analysed after 5 minutes with the procedure described in the example 1. Untreated candy and the rinsing solution obtained after taking the candy according to the procedure described earlier served as a blank sample.

The results can be seen in the Fig. 1.

Example 3

A candy containing therapeutic antibody was produced with the following procedure: 200 ml of water was heated to the boiling point and 5 g of agar (E 406) was added. The solution was boiled for 30 minutes to dissolve the agar. Thereafter 14,5 g of sugar, 3,7 g of xylitol and 50 g of cloud berry jam (Kesko, Finland) were added. The solution was froze to 55 °C and poured into a 7 ml mould, after which 25 mg of the antibody according to the example 1 was added in 0,4 ml saline solution. During the addition temperature was about 40 °C and the solution had started to solidify. The pH of the final candy was 4,27.

The test person took the candy and after that a sample was collected and analysed after 5 minutes according to the example 1. The blank sample was prepared before the actual sample according to the example 1 and it was analysed in a similar way.

The results can be seen in the Fig. 1.

Example 4.

Purified and lyophilized antibody, that had been produced specifically against *Francisella tularensis* in egg yolk according to the example 1, was added to sterile saline solution to the final concentration of the antibody of about 18 mg/ml. Xylitol was added to the solution to the final concentration of 100 mg/ml. Thereafter 250 µl of the solution obtained in this way was placed into the mouth-piece of a nipple, which was incised with a laboratory knife, and the antibody solution was shown to deafened onto the nipple surface through the incisions when the nipple was sucked.

Example 5

The volume of 400 µl of the antibody solution described in the example 4 was added

to 1 ml of Aqualan L (Orion, Helsinki) cream and they were mixed carefully. The emulsion was then spread to the skin and the mucous membranes of mouth. Preservation of the antibody in an active form after spreading was demonstrated with different immunological methods.

5 The results from examples 1,2 and 3 (Elisa-method) are presented in the figure 1. The control shows the situation, where 25 mg of antibody was added to 10 ml of physiological saline solution and 50 µg/l of this sample was taken and analysed in a way described in the example 1. The results show that lowering the pH decreases the
10 biological binding ability of the antibody. In a similar way the regulation of pH (buffering) preserves the biological ability of the antibody. When the antibody is casted in agarose (cloud berry marmalade), high sugar content supports the biological activity of the antibody in low pH. The results show, that the ability of antibodies to function on the mucous membranes had been preserved.

15 The invention will not be limited to the applications presented here, but it can change within the idea of patent claims.

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CLAIMS

1. Therapeutic and preventive method against harmful microbes and substances, where antibodies will be produced in eggs, and will be isolated from their yolk, characterized in, that the specific antibody against harmful microbes or substances will be transported to the organism as a product which is to be sucked or chewed, or is in a liquid form, or is cream or emulsion.

2. Method according to the claim 1 characterized in, that antibody is placed into the organism together with a probiotic microbial strain.

3. Method according to the claim 1 characterized in, that probiotic microbe cells, medical substances, enzymes or other corresponding components have been joined to IgY-antibody molecules produced in the egg yolk from the mannose molecule that is situated in their Fc part.

4. Method according to the claim 1 characterized in, that antibody is placed in sweets, chewing gum or other products like that.

5. Method according to the claim 1 characterized in, that antibody is placed in the form of liquid, emulsion or cream on or in a nipple and on a nipple there are paths, incisions, semipermeable surfaces or other structures through which liquid, emulsion or cream can seep into the mouth when the nipple is sucked.

6. Method according to the claim 2 or 3 characterized in, that antibody or microbial strain is placed into sweets, chewing gum and corresponding products.

7. Method according to the claim 1 characterized in, that the antibody or microbial strain is placed in the form of liquid, emulsion or cream on or in a nipple and on a nipple there are paths, incisions, semipermeable surfaces or other structures through which liquid, emulsion or cream can seep to mouth when the nipple is sucked.

8. Method according to the claim 1-3 characterized in, that antibody or probiotic microbial strain is placed in a marmalade candy or other gel-like candy.

9. Method according to the claim 1-3 characterized in, that antibody or probiotic microbial strain is placed in a marmalade candy or other gel-like candy in temperatures under 45 °C.

5 10. Method according to the claim 1-3 characterized in, that antibody or probiotic microbial strain is placed in a marmalade candy or other gel-like candy in temperatures under 55 °C.

10 11. Method according to the claim 1-2 characterized in, that antibody or probiotic microbial strain is placed in cream, emulsion or other product like that is spread to the skin or mucous membranes.

12. Method according to the claim 1-10 characterized in, that antibody is placed in a product, where the pH has been buffered.

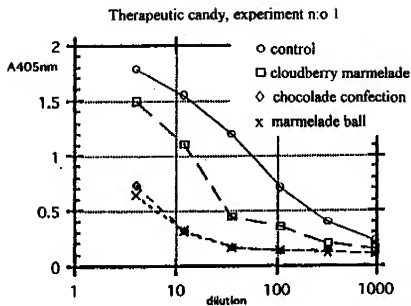
15 13. Method according to the claim 1-10 characterized in, that antibody is placed in liquid form containing trehalose molecules or other molecules that protect it from high temperatures.

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Figure 1.



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/FI 97/00208

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/00, A61K 39/395, A23G 3/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CLAIMS, USPATFULL, EMBASE, MEDLINE, BIOSIS, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 01162916, WPI accession no. 97-140841/199713, LOTTE CO LTD: "Chewing gum to prevent e.g. oral infection - contains egg antibody added to chemical gum base"; & JP,A,9020684 19970121 --	1-13
X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 008015737, WPI accession no. 89-280849/198939, GEN CORP KK et al: "Antibody used to prevent dental caries - where immunoglobulin fraction isolated from egg yolk inhibits streptococ- cus mutans from producing plaque"; & JP,A,1203317 19890816 --	1-13

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

Date of mailing of the international search report

22 August 1997

25-08-1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 97/00208

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9421284 A1 (PHARMA PACIFIC PTY. LTD.), 29 Sept 1994 (29.09.94), page 7, line 2-12, line 30-35 --	1-13
X	DE 4324859 A1 (LION CORP.), 27 January 1994 (27.01.94), page 5, line 34-52, claim 7 --	1-13
X	WO 9315736 A1 (PHARMOS CORP.), 19 August 1993 (19.08.93), page 18, line 5-18, claim 15 --	1-13
X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 008958579, WPI accession no. 92-085848/199211, TAKARA SHUZO CO LTD: "Skin cosmetic with prolonged effect - contains (modified) antibody and usual carrier"; & JP,A,4029912 19920131 --	1-13
X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 008062519, WPI accession no. 89-327631/198945, GEN CORPORATION KK: "Antibody, for preventive agents for cariogenic teeth - compris- es immunoglobulin prepd. from eggs of chickens immunised with water-insol. glucan synthetic enzyme; & JP,A,1242534 19890927 -- -----	1-13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 97/00208

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 1-13 are directed to methods of treatment of the human or animal body therapy method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims.
The search has been based on the alleged effects of the compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/08/97

International application No.

PCT/FI 97/00208

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